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GUIDELINE RECOMMENDATIONS AND ANTIMICROBIAL RESISTANCE: THE NEED FOR A CHANGE

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Abstract

Objectives: Antimicrobial resistance has become a global burden for which inappropriate antimicrobial use is an important contributing factor. Any decisions on the selection of antibiotics use should consider their effects on antimicrobial resistance. The objective of this study was to assess the extent to which antibiotic prescribing guidelines have considered resistance patterns when making recommendations for five highly-prevalent infectious syndromes.

Design: We used Medline searches complemented with extensive use of Web engine to identify guidelines on empiric treatment of community-acquired pneumonia, urinary tract infections, acute otitis media, rhinosinusitis and pharyngitis. We collected data on microbiology and resistance patterns, and identified discrete pattern categories. We assessed the extent to which recommendations considered resistance, in addition to efficacy and safety, when recommending antibiotics.

Results: We identified 135 guidelines, which reported a total of 251 recommendations. Most (103, 79%) were from developed countries. Community-acquired pneumonia was the syndrome mostly represented (51, 39%). In only 16 (6.4%) recommendations, selection of empiric antibiotic was discussed in relation to resistance and specific microbiologic data. In a further 69 (27.5%) recommendations, references were made in relation to resistance, but the attempt was inconsistent. Across syndromes, twelve patterns of resistance with implications on recommendations were observed. Fifty to 75 % of recommendations did not attempt to set recommendation in the context of these patterns.

Conclusion: There is consistent evidence that guidelines on empirical antibiotic use did not routinely consider resistance in their recommendations. Decision makers should analyze and report the extent of local resistance patterns to allow better decision-making.

Strengths and limitations of the study

- Antimicrobial resistance is a public health priority worldwide and avoidance of inappropriate use of antibiotics has become an urgent need. As the adoption of guidelines targeting antibiotic prescribing has been associated with large benefits, it is important to monitor guidelines to identify areas of improvements, such as minimization of development of resistance.
- As part of the World Health Organization Global Action Plan on Antimicrobial Resistance, this study is an innovative comparison of guidelines on the appropriate use of antibiotics based on resistance patterns.
- Research was limited only to an electronic screening so printed versions of clinical practice guidelines may have been missed.
- Recommendations were arbitrarily hierarchized according to the influence of resistance data collected.
- Further research on the quality and relevance of specific recommendations based on resistance is needed identifying further obstacles to progress antimicrobial resistance and bringing them to light.

Background

The appropriate use of antibiotics has become a worldwide priority. In 2000 globally it was estimated 54 billion standard units of antibiotics have been consumed and this figure increased by 36% in the following 10 years, creating the preconditions of a public health crisis[1,2]. This problem is not confined to high and middle income countries where antibiotics are considered as an undeniable right, but it is also accentuated in low income countries where antibiotics are becoming part of a consumerist approach to health care; e.g. the use of antibiotics is four-fold in India than in Scandinavian countries[3,4]. Inappropriate prescribing, over-the-counter sales of antibiotics and high consumption contributed to an increase in bacterial selection pressure. Time trend analyses have reported an increase in antimicrobial resistance (AMR) including extended spectrum β-lactamase, Gram negative bacteria resistant to carbapenems, or plasmid mediated colistin resistance[5]. Such resistance patterns have been associated with negative outlooks on clinical and public health burden, including deaths, attributable to AMR[6].

In the last twenty years, there has been an emphasis on the need to modify prescribers' behaviors: guidelines emerged as an intervention to support clinical decision making through a consensual process based on evidence, and reinforce collective action to tackle relevant disease problems[7]. The adoption of guidelines targeting antibiotic prescribing, a medical behavior characterized by scarce diligence, has been associated with large benefits, encompassing both improvement in mortality[8] and in resistance[9]. Conscious scientific societies can contribute to control AMR by producing necessary, appropriate, and specific recommendations to optimize the use of antibiotics, and inviting health professionals to adhere to them.

We hypothesized that scientific societies and professional associations invested time and energies finalizing guidelines to provide information on empiric antibiotic use. We assumed that these guidelines have at the core resistance threats and report information on country specific resistance patterns, as these are essential information to guide the empiric choice of antibiotics. Therefore we mapped guidelines targeting five common infectious conditions where empiric therapy prevails, and evaluated what proportion of recommendations consider resistance patterns as a driver of the clinical decision making, how resistance influences recommendations and whether resistance can be better incorporated.

Methods

This cross-sectional study is part of a large comprehensive review of antibiotics that aims to revise the selection of antibiotics included in the 2017 World Health Organization (WHO) Model List of

Essential Medicines, and is part of the 2015 Global Action Plan on Antimicrobial Resistance[10], a series of international actions to monitor and control antibiotics resistances.

Identification of guidelines

A guideline was eligible for inclusion if the publication type was a clinical practice guideline (CPG) consistent with the standard definition - "*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*"[11].

A systematic search for CPGs of antibiotic therapy for five infectious disease syndromes - community-acquired pneumonia (CAP), urinary tract infections (UTIs), acute otitis media (AOM), rhinosinusitis (RHI) and pharyngitis (PHA) - was conducted. We selected these diseases as a purposive sample of twenty-five syndromes considered in the comprehensive Essential Medicine List review. They represent the most prevalent infectious diseases worldwide, a balanced case mix of benign and severe diseases, and cover the spectrum of empirical antibiotic treatment choices.

To our knowledge, there is no single repository of CPGs on antibiotics. Therefore, in order to retrieve relevant CPGs, we first performed a Medline search using "clinical practice guideline" and its variations in the title and as key words, and the name of the syndrome and its variations. Secondly we used Google as the search engine to explore documents that are not reported in the medical literature but available on the Internet assuming that a relevant number of guidelines would have been possibly published by scientific societies or governmental agencies and released on the Internet, but not captured by Medline or formal literature repositories. All searches were made using country-specific or local Google versions[12]. So, for instance, French guidelines were searched on the local version of the Google page—Google.fr. For each website of a potential CPG issuer (e.g. scientific society), one reviewer retrieved CPGs through an analysis of the official website. We finally searched the WHO Essential Medicines and Health Products Information Portal[13], an online repository of full-text publications on medicines and health products related to WHO priorities, other United Nations (UN) partners, global Non-Governmental Organizations (NGOs), development agencies and their partners, countries and academics. Resources within the portal were filtered with the help of the WHO information specialist in charge of organizing the portal information.

Our searches were conducted during the period June - July 2016. No date, language or age restrictions were applied.

Systematic reviews, meta-analyses as well as consensus conferences were excluded. Duplicated and guidelines superseded by more recent version were also removed.

Information sought for each guideline

For each included guideline, we sought general information about the country of origin, its income and geographical place according to the WHO regions, infectious syndrome, year of publication, target population, promoting institution, and financial support.

Influence of resistance patterns over recommendations

In order to be included in the descriptive analysis, a CPG had to provide recommendations on the empiric use of antibiotic treatments for at least one syndrome. We used the standard definition of recommendation of the WHO. That implies a choice between different interventions - antibiotics in the actual study - that have an impact on health and that have implications for the use of resources[14].

It is important to notice that each CPG can present recommendations across multiple syndromes. We considered each recommendation on antibiotic use as a potential opportunity to incorporate resistance pattern information (i.e. desirable criterion). We assumed that patterns should be included in any recommendations about optimal use of antibiotics, the most conservative scenario being that a recommendation clearly excludes relevant resistance, and then recommends preferred antibiotic choice with a curative intent, considering avoidance of further development or spread of resistance. An example is recommending first-line antibiotic therapy amoxicillin or amoxicillin with clavulanate (alternative) for otitis media. Complex scenarios would consider, for instance, the recommendation of alternative antibiotics based on resistance thresholds.

Recommendations were classified according to the influence of epidemiologic and resistance patterns data on recommendations in three ordinal categories: satisfactory, partial satisfactory and unsatisfactory (Table 1). They were considered as satisfactory if they provided a list of empirical antibiotics modulated by complete and country-level collected data on microbiological and resistance patterns. In fact, we arbitrarily postulated that recommendations about optimal antibiotic use should consider country-specific resistance patterns as a key driver of the selection of antibiotic. Resistance patterns had to be consistently reported across recommendations targeting antibiotic use for a syndrome. Partially satisfactory recommendations had some but not all of the resistance pattern information, or used this information inconsistently across recommendations. Lastly, recommendations were classified as unsatisfactory when: they did not use epidemiologic and resistance data to justify antibiotic selection, recommendations were de-linked from resistance patterns, or these were not country-specific.

For each guideline, one reviewer independently retrieved information through an analysis of the document. The same reviewer also classified the satisfactory level based on the completeness of resistance patterns information. Different patterns were collegially discussed and doubts were resolved by discussion.

For each infectious syndrome, we identified discrete characteristics of resistance with implications on recommendations. In other words, if a recommendation contained data on resistance, it could generate guidance based on such resistance patterns, suggesting appropriate or inappropriate antibiotics (e.g. using a specific antibiotic such as amoxicillin-clavulanate in case of risk of bacterial strains producing β-lactamase in mild CAP). We then calculated how many recommendations failed to consider discrete patterns, reporting median and interquartile range as measures of distribution.

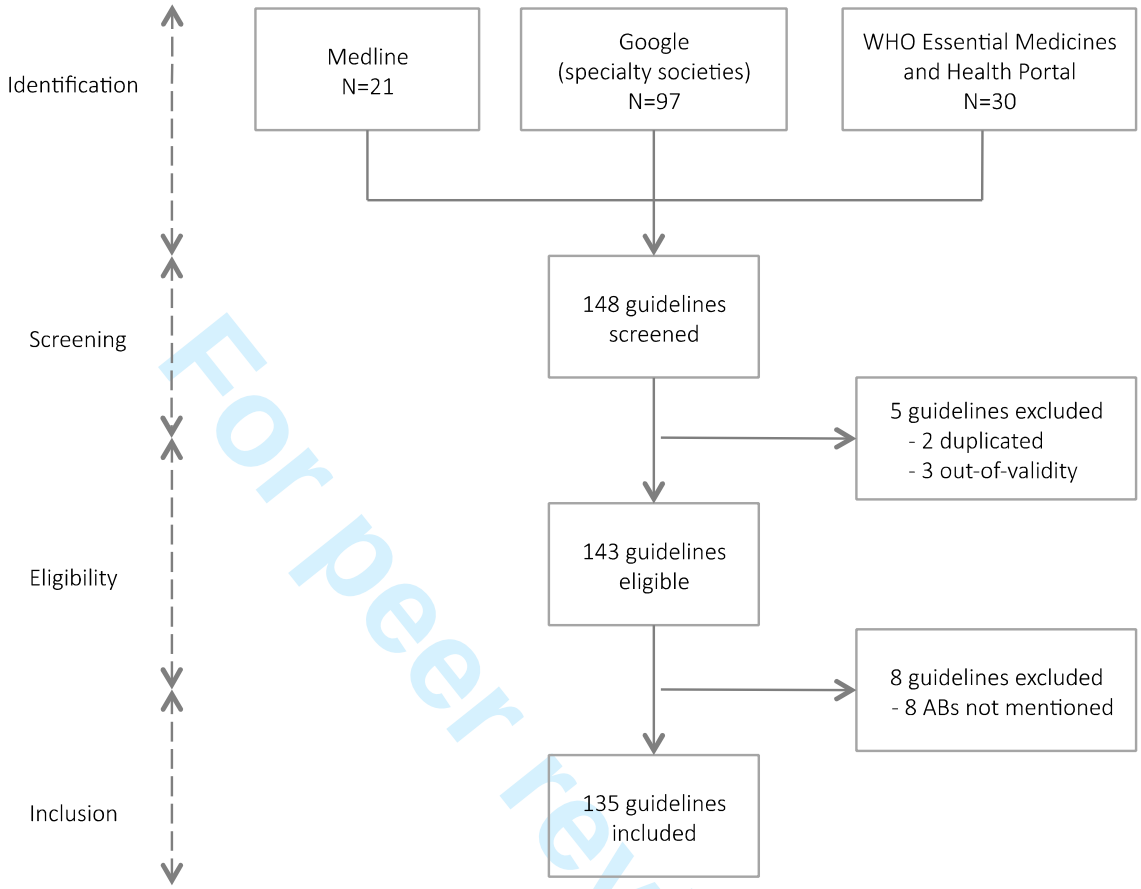
Table 1. Hierarchy of the recommendations

Level of satisfaction of recommendations	Desirable criterion	Illustration
Satisfactory	Empiric antibiotic recommendation was supported by country-specific resistance patterns	Management for uncomplicated cystitis in women in Sweden listed recommendations for preferred antibiotics. For instance, nitrofurantoin was a preferred option as a first line treatment because of low resistance rates in a community setting whereas fluoroquinolones were not indicated in this syndrome due to rapidly increasing resistance development[15]. American recommendations for bacterial rhinosinusitis recommend high-dose amoxicillin as a preferred option over standard-dose amoxicillin primarily to cover and control penicillin resistant *Streptococcus pneumoniae* (PRSP)[16].
Partial satisfactory	Empiric antibiotic recommendation was supported by inconsistent resistance patterns	Filipino recommendations for mild CAP recommended the use of a βLactam with a βlactamase inhibitor without any justification on resistance. However, macrolides were considered as an alternative treatment because of a high threshold of resistance (20% resistance rate) among population[17].
Unsatisfactory	Empiric antibiotic recommendation did not support any resistance patterns or was not justified by country-specific resistance patterns	βlactams as well as macrolides were recommended for the management of pharyngitis in Namibia without any specification about microbiology or resistance[18].

Results

We retrieved 148 CPGs: 21 (14%) from Medline, 97 (66%) from websites of specialty societies and 30 (20%) from the WHO Essential Medicines and Health Products Information Portal. Of these CPGs, 135 (91%) met our inclusion criteria and were described in details, and provided sufficient information for qualitative evaluation. Thirteen guidelines were excluded because no recommendation on empiric treatment was made, or were duplicates or out-of-validity guidelines (Figure 1).

Figure 1. Flow chart of CPGs



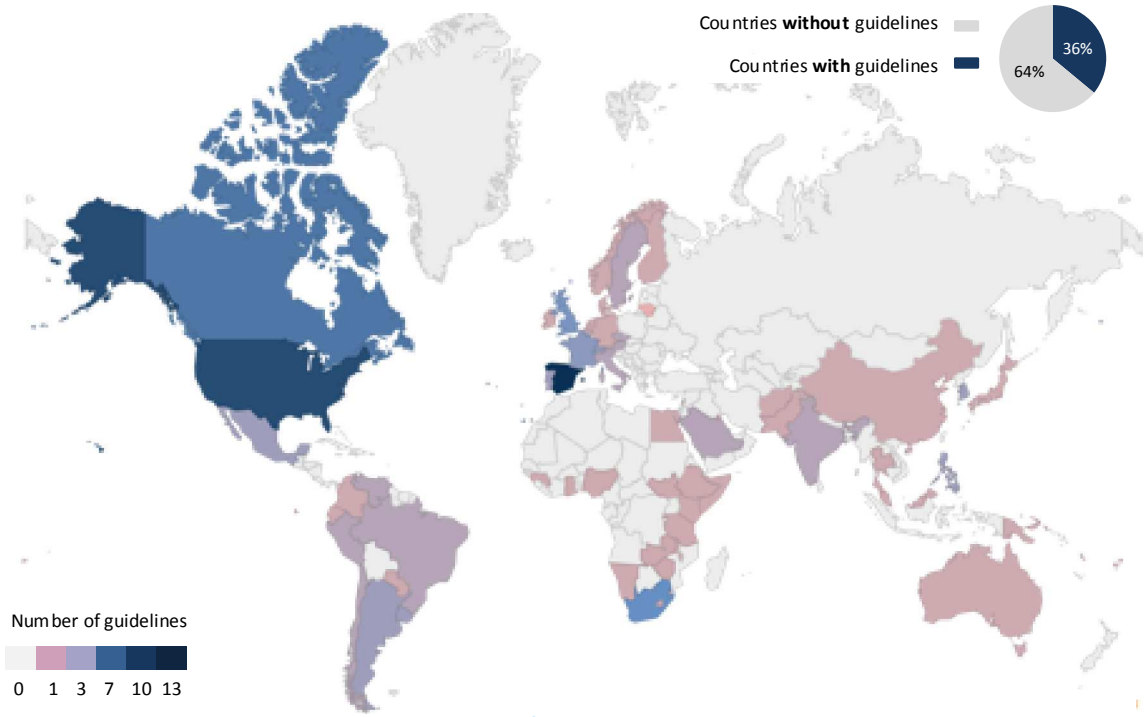
General characteristics of the guidelines are summarized in Table 2. Among the 194 United Nations Member States, 70 (36%) provided guidelines of at least one of the five syndromes. The majority (106, 79%) of the CPGs arose from high and upper middle-income countries whereas lower middle and low-income countries contributed marginally (28, 21%). EURO and PAHO were the two most represented WHO regions, originating 44 (33%) and 39 (29%) CPGs respectively. Among the five infectious syndromes studied, CAP's treatment was the top-ranked syndrome in the agenda (51, 39%), followed by UTI (42, 31%). Half of the CPGs were published between 2011 and 2016. Figure 2 shows the geographical distribution of guidelines across the 194 United Nations Member States.

Table 2. General characteristics of the CPGs

	n	%
Total	135	
Income*		
High Income Country (HIC)	78	58%
Upper Middle Income Country (UMIC)	28	21%
Lower Middle Income Country (LMIC)	17	13%
Low Income Country (LIC)	11	8%
WHO region*		
African Regional Office (AFRO)	23	17%
Eastern Mediterranean Regional Office (EMRO)	8	6%
European Regional Office (EURO)	44	33%
Pan American Regional Office (PAHO)	39	29%
South East Asia Regional Office (SEARO)	3	3%
West Pacific Regional Office (WPRO)	16	12%
Syndromes		
Community Acquired Pneumonia	51	39%
Urinary Tract Infections	42	31%
Acute Otitis Media	16	12%
Rhinosinusitis	14	10%
Pharyngitis	12	8%
Year of publication		
Median (IQR)	2011 (2008-2013)	
Min-Max	2000-2016	

* Total of 133, European Union was not part of a WHO region or the World Bank classification[19]

Figure 2. Geographical distribution of CPGs (n=135).



A total of 251 recommendations were identified: these subgrouped by syndromes will be considered the denominators in the following analyses.

Compliance with our desirable criteria is presented in Table 3. Only a minority of the recommendations – 16 (6.4%) – was classified as satisfactory (i.e. including or mentioning resistance) whereas 69 (27.5%) and 166 (66.1%) recommendations partially or totally omitted data on microbiological resistance respectively. Guidelines that incorporated resistance on all recommendations originated from France[20], Sweden[21] and the United States[16,22].

Descriptive analysis of the resistance patterns is shown in Table 4. Of the 12 discrete patterns how resistance may influence recommendations, ten patterns were identified for CAP, six for UTI, seven for rhinosinusitis and acute otitis media and finally four for pharyngitis. Looking at the distribution of resistance into recommendations, 50 to 75% of recommendations failed to mention resistance patterns in the antibiotic guidance when these patterns might have had an impact.

For CAP, the risk for atypical pathogens was addressed in 26% of the recommendations. Multi-drug resistance concerns, however, were covered only in 1.4% of recommendations. Resistance patterns in UTI recommendations ranged from two to five, and nine (14.3%) UTI recommendations described alternative antibiotics based on resistance threshold.

No satisfactory recommendation was identified for the management of pharyngitis. Resistance is rare in the most common pathogens for bacterial pharyngitis, thus, only one resistance pattern by pharyngitis' recommendations was found.

Of all recommendations, alternative antibiotic therapy was observed for all syndromes where fluoroquinolones appeared to be the most frequent alternative antibiotic in CAP (11%) and UTIs (12.7%) (Suppl. Table 1 and 2).

Table 3.Compliance with desirable resistance criteria of recommendations, subgrouped by syndrome.

Hierarchy of recommendations	**CAP**	**UTI**	**AOM**	**RHI**	**PHA**	**Total**
Satisfactory	4 (5.5%)	5 (7.9%)	3 (7.1%)	4 (10.2%)	0 (0%)	16 (6.4%)
Partial satisfactory	31 (42.5%)	11 (17.4%)	11 (26.2%)	6 (15.4%)	10 (29.4%)	69 (27.5%)
Unsatisfactory	38 (52.0%)	47 (74.6%)	28 (66.7%)	29 (74.4%)	24 (70.6%)	166 (66.1%)
Total	73	63	42	39	34	251

CAP: Community Acquired Pneumonia, **UTI**: Urinary Tract Infections, **AOM**: Acute otitis media, **RHI**: Rhinosinusitis, **PHA**: Pharyngitis

Table 4. Descriptive analysis of resistance patterns in the recommendations grouped by syndrome (n=251)

	CAP	UTI	AOM	RHI	PHA
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	14 (19.2%)	9 (14.3%)	5 (11.9%)	3 (7.7%)	1 (2.9%)
Antibiotic not indicated because of high resistance rate	2 (2.7%)	6 (9.5%)	1 (2.4%)	3(7.7%)	5 (14.7%)
Resistance risk	12 (16.4%)	7 (11.1%)	4 (9.5%)	3 (7.7%)	_
Resistance threshold	_	9 (14.3%)	_	2 (5.1%)	2 (5.9%)
Resistance AB	_	5 (7.9%)	_	_	_
Resistance dosage	8 (11.0%)	_	7 (16.7%)	8 (20.5%)	_
Atypical pathogens	19 (26.0%)	_	_	_	1 (2.9%)
MRSA risk	7 (9.6%)	_	_	_	_
MDR risk	1 (1.4%)	5 (7.9%)	1 (2.4%)	_	_
PRSP risk	6 (8.2%)	_	6 (14.3%)	5 (12.8%)	_
Aeru risk	14 (19.2%)	_	_	_	_
B-lactamase risk	8 (11.0%)	_	11 (26.2%)	7 (17.9%)	_
Discrete resistance patterns mentioned in recommendations					
Total	10	6	7	7	4
Median					
n	3	2	2	3.5	1
%	30.0 %	33.3%	28.6%	50.0%	25.0%
Interquartile range					
n	[2-3]	[2-5]	[1.3-3]	[1.7-4]	[1-1]
%	[20%-30%]	[33.3%-83.3%]	[17.9%-42.9%]	[21.4%-57.1%]	[25%-25%]

CAP: Community Acquired Pneumonia ; **UTI**: Urinary Tract Infections ; **AOM**: Acute otitis media ; **RHI**: Rhinosinusitis ; **PHA:** Pharyngitis ; **Resistance risk** : Antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months) ; **Resistance threshold** : Antibiotic used only under a certain threshold of resistance ; **Resistance AB** : Antibiotic used if first line AB is resistant ; **Resistance dosage** : Antibiotic used at high dosage if there is a risk of resistant strains ; **Atypical pathogens** : Risk of atypical pathogens ; **MRSA risk** : Risk of meticillin-resistant *Staphylococcus aureus* (MRSA) ; **MDR risk :** Risk of Multi Drug Resistant strains ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumoniae* (PRSP) ; **Aeru risk** : Risk of *Pseudomonas aeruginosa* ; **βlactamase risk** : Risk of strains producing βlactamase

Discussion

In view of the post-antibiotic era and the global burden of antibiotic resistance worldwide, it is important that recommendations consider (in)appropriate antibiotics when there is an opportunity to reduce resistance. This review found an important gap in antibiotics guidelines: resistance

patterns were not considered by two third of recommendations for five highly prevalent infectious syndromes. Moreover, less than 10% of all recommendations consistently reported data on their country specific resistance patterns. The recommendation would serve better the medical community if a specific antibiotic is preferred over the others, with the aim of providing appropriate coverage and minimizing spread and development of resistance. If resistance is not considered in guideline development, it is unlikely to be considered downstream. These data imply that significant changes are needed to the way resistance data is considered in recommendations for antibiotics.

Given the scarce attention to resistance, it is not surprising that evidence of substantial inappropriate or overuse of non-first-line antibiotics for most common conditions is prevalent in the medical literature. For instance data from the United States indicates that the problem of inappropriate antibiotic prescribing includes not only prescriptions that are unnecessary altogether, but also inappropriate selection of agents: physicians prescribed inappropriate antibiotics in about 30% to 50% of ambulatory adult consultations with suspected common infectious diseases[23,24]. However, when guidance is provided, evidence shows a more conscious use of antibiotics[25]. Since large areas of the world lack the infrastructure to collect resistance data, countries in need should be supported through international projects such as ReAct[26] or Ecumenical Pharmacy Network[27]. In the move towards better management of resistance, there is room for better standardization of approaches to include resistance on recommendations and better reporting of resistance data. Panels should scrutinize country-specific resistance data when considering antibiotic recommendations and should report the data, including important time trends. Guidelines certainly deserve attention, but implementation and quality improvement interventions are also important. Indeed, education and incentives that facilitate antibiotic optimal prescription should also be sustained by adequate policies. The quality of guidelines is closely intertwined with the quality of reporting. It is possible that guidelines took resistance patterns into consideration in their recommendations without mentioning it. Lack of details on how recommendations were developed leads users to assume that the quality was inadequate, unless information to the contrary is provided[28]. This is often justified because faulty reporting generally reflects faulty methods[29].

Although some findings are worrisome, other look more positive. One third of countries had at least one guideline on antibiotic use: even in the absence of published data, this number suggests that the guideline panels invested a remarkable amount of energy in this field. Fourteen countries produced more than 2 guidelines for at least one syndrome, raising concerns for duplication of efforts. The more prolific country, Spain, had a production of 13 documents, likely to generate redundancy and confusion. Most guidelines were from high-income countries, with low- and lower-middle-income countries providing only 21%. Weak health care systems, including inadequate infrastructures for

resistance collection, may justify the absence of epidemiologic and resistance data in these countries. Resistance patterns are highly heterogeneous: patterns in upper respiratory tract infections are limited in comparison with UTIs or CAPs. In the latter antibiotics and resistance may play a substantial role avoiding an evolution into life-threatening diseases. Paucity of resistance data in UTIs can be explained by the high probability of a viral etiology and a benign disease decourse. Antibiotics are not recommended as treatment by many scientific societies: the NICE guidelines (UK) did not include any antibiotic therapy in their guidance for these 3 syndromes[30]. This approach converges with the concept of wait and see prescription, to reduce unnecessary antibiotics use, which demonstrated to be efficient in the treatment of acute otitis media in children[31].

We recognize that our study can provide nothing more than a snapshot of the current state of the recommendations related to one dimension, antibiotic resistance. Comprehensive user-centered evaluations of the overall quality of guideline are needed. It was not our aim to assess whether recommendations have improved or worsened over time. Rather we sought to assess whether a problem existed at the time of our study. We did not investigate if recommendations on discrete resistance patterns were correct, or supported by evidence. The relevance of resistance patterns was not weighted. We accepted study authors' guidance on discrete patterns at face value, without further evaluating the quality of the recommendation. We adopted a non-validated arbitrary ordinal scale. Searches were done by a single researcher. We did not consider paper-based guidelines, which might be still prevalent in some contexts. Further research on the quality and relevance of specific recommendations based on resistance is needed identifying further obstacles to progress AMR and bringing them to light.

Conclusion

Our findings revealed that guidelines on empirical use of antibiotics do not provide meaningful information on resistance patterns and interpretation by decision makers is difficult because – as a principle – local resistance patterns should always be considered with empiric antibiotic choices. In appraising the evidence for antibiotic use guideline developers should be aware of the breadth and depth of overarching resistance issues. Awareness and understanding of AMR through surveillance and research are pillars of the WHO Global Action Plan on Antimicrobial Resistance. These results can be used by global initiatives such as the U.N. General Assembly High-Level Meeting on Antimicrobial Resistance and the Conscience of Antimicrobial Resistance Accountability (CARA) Alliance to monitor progress.

List of Abbreviations

AB: Antibiotic

ABL: Apparented to β-lactam

AMN: Aminoglycoside

AMR: Antimicrobial Resistance

AOM: Acute Otitis Media

BLA: β-lactam

CAP: Community-Acquired Pneumonia

CAR: Carbapenem

CPG: Clinical Practice Guideline

EMRO: Eastern Mediterranean Regional Office

EURO: European Regional Office

FOF: Fosfomycin derivative

FQL: Fluoroquinolone

GLY: Glycopeptide

HIC: High-income Country

IMD: Imidazole derivative

IQR: Interquartile Range

LIC: Low-income Country

LMIC: Lower-middle Income Country

MDR: Multi Drug Resistant

MLS: Macrolide, Lincosamide, Streptogramin

MON: Monobactam

MRSA: Meticillin Resistant *Staphylococcus aureus*

NGO: Non-Governmental Organization

NICE: National Institute for Health and Care Excellence

NTF: Nitrofuran derivative

OXZ: Oxazolidinone

PAHO: Pan American Health Organization

PHA: Pharyngitis

PHE: Amphenicol

PRSP: Penicillin resistant *Streptococcus pneumoniae*

RHI: Rhinosinusitis

SEARO: South East Asia Regional Office

TET: Tetracycline

TMP: Trimethoprim derivative

UK: United Kingdom

UMIC: Upper-middle Income Country

UN: United Nations

URTI: Upper Respiratory Tract Infection

UTI: Urinary Tract Infection

WHO: World Health Organization

WPRO: West Pacific Regional Office

Ethics

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

CE, LM, DM, ML, GF and NM declare that they have no competing interests.

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Author's contribution

All authors made a substantial contribution to the conception and the design of the study. CE contributed to literature search and data collection. CE and LM contributed to the analysis. All authors participated in the interpretation of data. CE and LM drafted the initial manuscript. NM and GF coordinated the study. CE, LM, DM, ML, GF, and NM contributed to the review of the manuscript. All authors read and approved the final manuscript.

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ANNEXES

Supplementary Table 1. Antibiotic and resistance patterns in Community-Acquired Pneumonia (n=73)

	AMN	BLA	CAR	FQL	GLY	IMD	MLS	OXZ	PHE	TET	TMP
Recommendations considering resistance patterns											
Antibiotic used as an alternative because of high resistance rate	_	4(5.5%)	2(2.7%)	8(11.0%)	_	_	8 (11.0%)	_	_	5(6.8%)	1(1.4%)
Antibiotic not indicated because of high resistance rate	_	_	_	1(1.4%)	_	_	1 (1.4%)	_	_	1(1.4%)	_
Resistance risk	_	10(13.6%)	1(1.4%)	8(11.0%)	_	1 (1.4%)	5 (6.8%)	_	_	1(1.4%)	_
Resistance dosage	_	8(11.0%)	_	_	_	_	_	_	_	_	_
Atypical pathogens	_	_	_	2(2.7%)	_	_	17 (23.3%)	_	1(1.4%)	11(15%)	1(1.4%)
MRSA risk	_	_	_	_	5(6.8%)	_	3 (4.1%)	6(8.2%)	_	1(1.4%)	_
MDR risk	_	_	1(1.4%)	_	_	_	1 (1.4%)	_	_	_	_
PRSP risk	_	7(9.6%)	_	2(2.7%)	_	_	1 (1.4%)	_	_	_	_
Aeru risk	9(12.3%)	14(19.1%)	12(16.4%)	10(13.7%)	_	_	9 (12.3%)	_	_	_	_
B-lactamase	1(1.4%)	7(9.6%)	_	1(1.4%)	_	1 (1.4%)	1 (1.4%)	_	_	_	_

AMN: Aminoglycosides; **BLA:** βlactam; **CAR**: Carbapenems; **FQL** : Fluoroquinolone ; **GLY** : Glycopeptids ; **IMD** : Imidazoles derivates ; **MLS** : Macrolides, Lincosamides, Streptogramins **; OXZ :** Oxazolidinones ; **PHE** : Amphenicoles : **TET** : Tetracyclines ; **TMP** : Trimetoprim derivates; **Resistance risk** : antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months) ; **Resistance dosage** : antibiotic used at high dosage if there is a risk of resistant strains ; **Atypical pathogens** : Risk of atypical pathogens ; **MRSA risk :** Risk of meticillin-resistant *Staphylococcus aureus* (MRSA) ; **MDR risk** : Risk of Multi Drug Resistant strains ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumonia* (PRSP) ; **Aeru risk** : Risk of *Pseudomonas aeruginosa* ; **βlactamase risk** :Risk of strains producing β-lactamase

Supplementary Table 2. Antibiotic and resistance patterns in Urinary Tract Infections (n=63)

	ABL	AMN	BLA	CAR	FOF	FQL	NTF	TMP
Recommendations considering resistance patterns								
Antibiotic used as an alternative because of high resistance rate	_	_	5 (7.9%)	_	1 (1.6%)	8(12.7%)	_	2(3.2%)
Antibiotic not indicated because of high resistance rate	_	_	5(7.9%)	_	_	2(3.2%)	_	1(1.6%)
Resistance risk	_	3 (4.8%)	1 (1.6%)	1 (1.6%)	_	2(3.2%)	2(3.2%)	1(1.6%)
Resistance AB	_	2 (3.2%)	2(3.2%)	_	1(1.6%)	1(1.6%)	_	1(1.6%)
Resistance threshold	1(1.6%	_	_	_	_	2(3.2%)	_	8 (12.7%)
MDR risk	_	2(3.2%)	_	2(3.2%)	_	_	_	_

ABL: Apparented to βlactam **; AMN**: Aminoglycosides ; **BLA :** βlactam ; **CAR** : Carbapenems; FOF : Fosfomycin derivates ; **FQL** : Fluoroquinolone ; **NTF:** Nitrofuran ; **TMP** : Trimetoprim derivates **; Resistance risk** : antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months) ; **Resistance threshold** : antibiotic used only under a certain threshold of resistance ; **Resistance AB** : antibiotic used if first line AB is resistant ; **MDR risk** : Risk of Multi Drug Resistant strains

Supplementary Table 3. Antibiotic and resistance patterns in Acute Otitis Media (n=42)

	BLA	FQL	MLS	OXZ	TMP
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	4 (9.5%)	_	3 (7.1%)	_	_
Antibiotic not indicated because of high resistance rate	_	_	_	_	1 (2.4%)
Resistance risk	4 (9.5%)	_	_	_	_
Resistance dosage	7 (16.7%)	_	_	_	_
MDR risk	_	1 (2.4%)	_	1 (2.4%)	_
PRSP risk	5 (11.9%)	_	1 (2.4%)	_	_
B-lactamase	11 (26.2%)	_	_	_	_

BLA : βlactam ; **FQL** : Fluoroquinolone ; **MLS** : Macrolides, Lincosamides, Streptogramins ; **OXZ :** Oxazolidinones ; **TMP** : Trimetoprim derivates ; **Resistance risk** : antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months); **Resistance dosage** : antibiotic used at high dosage if there is a risk of resistant strains ; **MDR risk** : Risk of Multi Drug Resistant strains ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumonia* (PRSP) ; **β-lactamase risk** :Risk of strains producing βlactamase

Supplementary Table 4. Antibiotic and resistance patterns in Rhinosinusitis (n=39)

	BLA	FQL	MLS	OXZ	TMP
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	1 (2.6%)	3 (7.7%)	_	_	_
Antibiotic not indicated because of high resistance rate	2 (5.1%)	_	3 (7.7%)	_	3 (7.7%)
Resistance risk	2 (5.1%)	2 (5.1%)	_	_	_
Resistance dosage	8(20.5%)	_	_	_	_
Resistance threshold	_	_	2 (5.1%)	_	_
PRSP risk	5(12.8%)	_	1 (2.6%)	1 (2.6%)	_
B-lactamase	8(20.5%)	_	_	_	_

BLA : βlactam ; **FQL** : Fluoroquinolone ; **MLS** : Macrolides, Lincosamides, Streptogramins ; **OXZ :** Oxazolidinones ; **TMP** : Trimetoprim derivates **; Resistance risk** : antibiotic used only if there is a risk of increasing resistance (recent use of critical AB during past months) ; **Resistance dosage** : antibiotic used at high dosage if there is a risk of resistant strains ; **Resistance threshold** : antibiotic used only under a certain threshold of resistance ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumonia* (PRSP) ; **β-lactamase risk** :Risk of strains producing β-lactamase

Supplementary Table 5. Antibiotic and resistance patterns in Pharyngitis (n=34)

	BLA	FQL	MLS	TET	TMP
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	1 (2.9%)	–	–	–	–
Antibiotic not indicated because of high resistance rate	2 (5.9%)	1 (2.9%)	–	2 (5.9%)	1 (2.9%)
Resistance threshold	–	–	2 (5.9%)	–	–
Atypical pathogens	–	–	1 (2.9%)	–	–

BLA : βlactam ; **FQL** : Fluoroquinolone ; **MLS** : Macrolides, Lincosamides, Streptogramins ; **TET** : Tetracyclins ; **TMP** : Trimetoprim derivates ; **Resistance threshold** : antibiotic used only under a certain threshold of resistance ; **Atypical pathogens** : Risk of atypical pathogens

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GUIDELINES AND ANTIMICROBIAL RESISTANCE: A SYSTEMATIC REVIEW ON NATIONAL RECOMMENDATIONS ON THE USE OF ANTIBIOTICS ACROSS UN MEMBER STATES

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GUIDELINES AND ANTIMICROBIAL RESISTANCE: A SYSTEMATIC REVIEW ON NATIONAL RECOMMENDATIONS ON THE USE OF ANTIBIOTICS ACROSS UN MEMBER STATES

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Abstract

Objectives: Antimicrobial resistance has become a global burden for which inappropriate antimicrobial use is an important contributing factor. Any decisions on the selection of antibiotics use should consider their effects on antimicrobial resistance. The objective of this study was to assess the extent to which antibiotic prescribing guidelines have considered resistance patterns when making recommendations for five highly-prevalent infectious syndromes.

Design: We used Medline searches complemented with extensive use of Web engine to identify guidelines on empiric treatment of community-acquired pneumonia, urinary tract infections, acute otitis media, rhinosinusitis and pharyngitis. We collected data on microbiology and resistance patterns, and identified discrete pattern categories. We assessed the extent to which recommendations considered resistance, in addition to efficacy and safety, when recommending antibiotics.

Results: We identified 135 guidelines, which reported a total of 251 recommendations. Most (103, 79%) were from developed countries. Community-acquired pneumonia was the syndrome mostly represented (51, 39%). In only 16 (6.4%) recommendations, selection of empiric antibiotic was discussed in relation to resistance and specific microbiologic data. In a further 69 (27.5%) recommendations, references were made in relation to resistance, but the attempt was inconsistent. Across syndromes, twelve patterns of resistance with implications on recommendations were observed. Fifty to 75 % of recommendations did not attempt to set recommendation in the context of these patterns.

Conclusion: There is consistent evidence that guidelines on empirical antibiotic use did not routinely consider resistance in their recommendations. Decision makers should analyze and report the extent of local resistance patterns to allow better decision-making.

Strengths and limitations of the study

- Antimicrobial resistance is a public health priority worldwide and avoidance of inappropriate use of antibiotics has become an urgent need. As the adoption of guidelines targeting antibiotic prescribing has been associated with large benefits, it is important to monitor guidelines to identify areas of improvements, such as minimization of development of resistance.
- As part of the World Health Organization Global Action Plan on Antimicrobial Resistance, this study is an innovative comparison of guidelines on the appropriate use of antibiotics based on resistance patterns across member states of United Nations.
- Research was limited only to an electronic screening so printed versions of clinical practice guidelines may have been missed.
- Recommendations were arbitrarily hierarchized according to the influence of resistance data collected.
- Further research on the quality and relevance of specific recommendations based on resistance is needed identifying further obstacles to progress antimicrobial resistance and bringing them to light.

Background

The appropriate use of antibiotics has become a worldwide priority. In 2000 globally it was estimated 54 billion standard units of antibiotics have been consumed and this figure increased by 36% in the following 10 years, creating the preconditions of a public health crisis[1,2]. This problem is not confined to high and middle income countries where antibiotics are considered as an undeniable right, but it is also accentuated in low income countries where antibiotics are becoming part of a consumerist approach to health care; e.g. the use of antibiotics is four-fold in India than in Scandinavian countries[3,4]. Inappropriate prescribing, over-the-counter sales of antibiotics and high consumption contributed to an increase in bacterial selection pressure. Time trend analyses have reported an increase in antimicrobial resistance (AMR) including extended spectrum β-lactamase, Gram negative bacteria resistant to carbapenems, or plasmid mediated colistin resistance[5]. Such resistance patterns have been associated with negative outlooks on clinical and public health burden, including deaths, attributable to AMR[6].

In the last twenty years, there has been an emphasis on the need to modify prescribers' behaviors: guidelines emerged as an intervention to support clinical decision making through a consensual process based on evidence, and reinforce collective action to tackle relevant disease problems[7]. The adoption of guidelines targeting antibiotic prescribing, a medical behavior characterized by scarce diligence, has been associated with large benefits, encompassing both improvement in mortality[8] and in resistance[9]. Conscious scientific societies can contribute to control AMR by producing necessary, appropriate, and specific recommendations to optimize the use of antibiotics, and inviting health professionals to adhere to them.

We hypothesized that scientific societies and professional associations invested time and energies finalizing guidelines to provide information on empiric antibiotic use. We assumed that these guidelines have at the core resistance threats and report information on country specific resistance patterns, as these are essential information to guide the empiric choice of antibiotics. Therefore we mapped guidelines targeting five common infectious conditions where empiric therapy prevails, and evaluated what proportion of recommendations consider resistance patterns as a driver of the clinical decision making, how resistance influences recommendations and whether resistance can be better incorporated.

Methods

This study is part of a large comprehensive review of antibiotics that aims to revise the selection of antibiotics included in the 2017 World Health Organization (WHO) Model List of Essential Medicines, and is part of the 2015 Global Action Plan on Antimicrobial Resistance[10], a series of international actions to monitor and control antibiotics resistances.

Identification of guidelines

A guideline was eligible for inclusion if the publication type was a clinical practice guideline (CPG) consistent with the standard definition - "*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*"[11].

A systematic search for CPGs of antibiotic therapy for five infectious disease syndromes - community-acquired pneumonia (CAP), urinary tract infections (UTIs), acute otitis media (AOM), rhinosinusitis (RHI) and pharyngitis (PHA) - was conducted. We selected these diseases as a purposive sample of twenty-five syndromes considered in the comprehensive Essential Medicine List review. They represent the most prevalent infectious diseases worldwide, a balanced case mix of benign and severe diseases, and cover the spectrum of empirical antibiotic treatment choices.

To our knowledge, there is no single repository of CPGs on antibiotics. Therefore, in order to retrieve relevant CPGs, we first performed a Medline search using the following terms "clinical practice guideline*" or "guideline*" in the title combined with the name of the syndrome as key words. For instance, looking at community-acquired pneumonia guidelines, we searched for "pneumonia" or "community acquired pneumonia" or "respiratory tract infection" or "lower respiratory tract infection". Secondly we used Google as the search engine to explore documents that are not reported in the medical literature but available on the Internet assuming that a relevant number of guidelines would have been possibly published by scientific societies or governmental agencies and released on the Internet, but not captured by Medline or formal literature repositories. All searches were made using country-specific or local Google versions[12]. So, for instance, French guidelines were searched on the local version of the Google page—Google.fr. For each website of a potential CPG issuer (e.g. scientific society), one reviewer retrieved CPGs through an analysis of the official website. We finally searched the WHO Essential Medicines and Health Products Information Portal[13], an online repository of full-text publications on medicines and health products related to WHO priorities, other United Nations (UN) partners, global Non-Governmental Organizations (NGOs), development agencies and their partners, countries and academics. Resources within the portal were

filtered with the help of the WHO information specialist in charge of organizing the portal information.

Our searches were conducted during the period June - July 2016. No date, language or age restrictions were applied.

Systematic reviews, meta-analyses as well as consensus conferences were excluded. Duplicated and guidelines superseded by more recent version were also removed.

Information sought for each guideline

For each included guideline, we sought general information about the country of origin, its income and geographical place according to the WHO regions, infectious syndrome, year of publication, target population, promoting institution, and financial support.

Influence of resistance patterns over recommendations

In order to be included in the descriptive analysis, a CPG had to provide recommendations on the empiric use of antibiotic treatments for at least one syndrome. We used the standard definition of recommendation of the WHO. That implies a choice between different interventions - antibiotics in the actual study - that have an impact on health and that have implications for the use of resources[14].

It is important to notice that each CPG can present recommendations across multiple syndromes. We considered each recommendation on antibiotic use as a potential opportunity to incorporate resistance pattern information (i.e. desirable criterion). We assumed that patterns should be included in any recommendations about optimal use of antibiotics, the most conservative scenario being that a recommendation clearly excludes relevant resistance, and then recommends preferred antibiotic choice with a curative intent, considering avoidance of further development or spread of resistance. An example is recommending first-line antibiotic therapy amoxicillin or amoxicillin with clavulanate (alternative) for otitis media. Complex scenarios would consider, for instance, the recommendation of alternative antibiotics based on resistance thresholds.

Recommendations were classified according to the influence of epidemiologic and resistance patterns data on recommendations in three ordinal categories: satisfactory, partial satisfactory and unsatisfactory (Table 1). They were considered as satisfactory if they provided a list of empirical antibiotics modulated by complete and country-level collected data on microbiological and resistance patterns. In fact, we arbitrarily postulated that recommendations about optimal antibiotic

use should consider country-specific resistance patterns as a key driver of the selection of antibiotic. Resistance patterns had to be consistently reported across recommendations targeting antibiotic use for a syndrome. Partially satisfactory recommendations had some but not all of the resistance pattern information, or used this information inconsistently across recommendations. Lastly, recommendations were classified as unsatisfactory when: they did not use epidemiologic and resistance data to justify antibiotic selection, recommendations were de-linked from resistance patterns, or these were not country-specific.

For each guideline, one reviewer independently retrieved information through an analysis of the document. The same reviewer also classified the satisfactory level based on the completeness of resistance patterns information. Different patterns were collegially discussed and doubts were resolved by discussion.

For each infectious syndrome, we identified discrete characteristics of resistance with implications on recommendations. In other words, if a recommendation contained data on resistance, it could generate guidance based on such resistance patterns, suggesting appropriate or inappropriate antibiotics (e.g. using a specific antibiotic such as amoxicillin-clavulanate in case of risk of bacterial strains producing β-lactamase in mild CAP). We then calculated how many recommendations failed to consider discrete patterns, reporting median and interquartile range as measures of distribution.

Table 1. Hierarchy of the recommendations

Level of satisfaction of recommendations	Desirable criterion	Illustration
Satisfactory	Empiric antibiotic recommendation was supported by country-specific resistance patterns	Management for uncomplicated cystitis in women in Sweden listed recommendations for preferred antibiotics. For instance, nitrofurantoin was a preferred option as a first line treatment because of low resistance rates in a community setting whereas fluoroquinolones were not indicated in this syndrome due to rapidly increasing resistance development[15]. American recommendations for bacterial rhinosinusitis recommend high-dose amoxicillin as a preferred option over standard-dose amoxicillin primarily to cover and control penicillin resistant *Streptococcus pneumoniae* (PRSP)[16].
Partial satisfactory	Empiric antibiotic recommendation was supported by inconsistent resistance patterns	Filipino recommendations for mild CAP recommended the use of a βLactam with a βlactamase inhibitor without any justification on resistance. However, macrolides were considered as an alternative treatment because of a high threshold of resistance (20% resistance rate) among population[17].
Unsatisfactory	Empiric antibiotic recommendation did not support any resistance patterns or was not justified by country-specific resistance patterns	βlactams as well as macrolides were recommended for the management of pharyngitis in Namibia without any specification about microbiology or resistance[18].

Results

We retrieved 148 CPGs: 21 (14%) from Medline, 97 (66%) from websites of specialty societies and 30 (20%) from the WHO Essential Medicines and Health Products Information Portal. Of these CPGs, 135 (91%) met our inclusion criteria and were described in details, and provided sufficient information for qualitative evaluation. Thirteen guidelines were excluded because no recommendation on empiric treatment was made, or were duplicates or out-of-validity guidelines (Figure 1).

General characteristics of the guidelines are summarized in Table 2. Among the 194 United Nations Member States, 70 (36%) provided guidelines of at least one of the five syndromes. The majority (106, 79%) of the CPGs arose from high and upper middle-income countries whereas lower middle and low-income countries contributed marginally (28, 21%). EURO and PAHO were the two most represented WHO regions, originating 44 (33%) and 39 (29%) CPGs respectively. Among the five infectious syndromes studied, CAP's treatment was the top-ranked syndrome in the agenda (51, 39%), followed by UTI (42, 31%). Half of the CPGs were published between 2011 and 2016. Figure 2 shows the geographical distribution of guidelines across the 194 United Nations Member States.

Table 2. General characteristics of the CPGs

	n	%
Total	135	
Income*		
High Income Country (HIC)	78	58%
Upper Middle Income Country (UMIC)	28	21%
Lower Middle Income Country (LMIC)	17	13%
Low Income Country (LIC)	11	8%
WHO region*		
African Regional Office (AFRO)	23	17%
Eastern Mediterranean Regional Office (EMRO)	8	6%
European Regional Office (EURO)	44	33%
Pan American Regional Office (PAHO)	39	29%
South East Asia Regional Office (SEARO)	3	3%
West Pacific Regional Office (WPRO)	16	12%
Syndromes		
Community Acquired Pneumonia	51	39%
Urinary Tract Infections	42	31%
Acute Otitis Media	16	12%
Rhinosinusitis	14	10%
Pharyngitis	12	8%

* Total of 133, European Union was not part of a WHO region or the World Bank classification[19]

A total of 251 recommendations were identified: these subgrouped by syndromes will be considered the denominators in the following analyses.

Compliance with our desirable criteria is presented in Table 3. Only a minority of the recommendations – 16 (6.4%) – was classified as satisfactory (i.e. including or mentioning resistance) whereas 69 (27.5%) and 166 (66.1%) recommendations partially or totally omitted data on microbiological resistance respectively. Guidelines that incorporated resistance on all recommendations originated from France[20], Sweden[21] and the United States[16,22].

Descriptive analysis of the resistance patterns is shown in Table 4. Of the 12 discrete patterns how resistance may influence recommendations, ten patterns were identified for CAP, six for UTI, seven for rhinosinusitis and acute otitis media and finally four for pharyngitis. Looking at the distribution of resistance into recommendations, 50 to 75% of recommendations failed to mention resistance patterns in the antibiotic guidance when these patterns might have had an impact.

For CAP, the risk for atypical pathogens was addressed in 26% of the recommendations. Multi-drug resistance concerns, however, were covered only in 1.4% of recommendations. Resistance patterns in UTI recommendations ranged from two to five, and nine (14.3%) UTI recommendations described alternative antibiotics based on resistance threshold.

No satisfactory recommendation was identified for the management of pharyngitis. Resistance is rare in the most common pathogens for bacterial pharyngitis, thus, only one resistance pattern by pharyngitis' recommendations was found.

Of all recommendations, alternative antibiotic therapy was observed for all syndromes where fluoroquinolones appeared to be the most frequent alternative antibiotic in CAP (11%) and UTIs (12.7%) (Suppl. Table 1 and 2). Proportions of resistance patterns according to antibiotic in acute otitis media, rhinosinusitis and pharyngitis are referenced in Suppl. Table 3, 4 and 5.

Table 3. Compliance with desirable resistance criteria of recommendations, subgrouped by syndrome.

Hierarchy of recommendations	CAP	UTI	AOM	RHI	PHA	Total
Satisfactory	4 (5.5%)	5 (7.9%)	3 (7.1%)	4 (10.2%)	0 (0%)	16 (6.4%)
Partial satisfactory	31 (42.5%)	11 (17.4%)	11 (26.2%)	6 (15.4%)	10 (29.4%)	69 (27.5%)
Unsatisfactory	38 (52.0%)	47 (74.6%)	28 (66.7%)	29 (74.4%)	24 (70.6%)	166 (66.1%)
Total	73	63	42	39	34	251

CAP: Community Acquired Pneumonia, **UTI**: Urinary Tract Infections, **AOM**: Acute otitis media, **RHI**: Rhinosinusitis, **PHA**: Pharyngitis

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Table 4. Descriptive analysis of resistance patterns in the recommendations grouped by syndrome (n=251)

	CAP	UTI	AOM	RHI	PHA
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	14 (19.2%)	9 (14.3%)	5 (11.9%)	3 (7.7%)	1 (2.9%)
Antibiotic not indicated because of high resistance rate	2 (2.7%)	6 (9.5%)	1 (2.4%)	3(7.7%)	5 (14.7%)
Resistance risk	12 (16.4%)	7 (11.1%)	4 (9.5%)	3 (7.7%)	_
Resistance threshold	_	9 (14.3%)	_	2 (5.1%)	2 (5.9%)
Resistance AB	_	5 (7.9%)	_	_	_
Resistance dosage	8 (11.0%)	_	7 (16.7%)	8 (20.5%)	_
Atypical pathogens	19 (26.0%)	_	_	_	1 (2.9%)
MRSA risk	7 (9.6%)	_	_	_	_
MDR risk	1 (1.4%)	5 (7.9%)	1 (2.4%)	_	_
PRSP risk	6 (8.2%)	_	6 (14.3%)	5 (12.8%)	_
Pseudomonas risk	14 (19.2%)	_	_	_	_
B-lactamase risk	8 (11.0%)	_	11 (26.2%)	7 (17.9%)	_
Discrete resistance patterns mentioned in recommendations					
Total	10	6	7	7	4
Median					
n	3	2	2	3.5	1
%	30.0 %	33.3%	28.6%	50.0%	25.0%
Interquartile range					
n	[2-3]	[2-5]	[1.3-3]	[1.7-4]	[1-1]
%	[20%-30%]	[33.3%-83.3%]	[17.9%-42.9%]	[21.4%-57.1%]	[25%-25%]

CAP: Community Acquired Pneumonia ; **UTI**: Urinary Tract Infections ; **AOM**: Acute otitis media ; **RHI**: Rhinosinusitis ; **PHA:** Pharyngitis ; **Resistance risk** : Antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months) ; **Resistance threshold** : Antibiotic used only under a certain threshold of resistance ; **Resistance AB** : Antibiotic used if first line AB is resistant ; **Resistance dosage** : Antibiotic used at high dosage if there is a risk of resistant strains ; **Atypical pathogens** : Risk of atypical pathogens ; **MRSA risk** : Risk of meticillin-resistant *Staphylococcus aureus* (MRSA) ; **MDR risk :** Risk of Multi Drug Resistant strains ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumoniae* (PRSP) ; **Pseudomonas risk** : Risk of *Pseudomonas aeruginosa* ; **βlactamase risk** : Risk of strains producing βlactamase

Discussion

In view of the post-antibiotic era and the global burden of antibiotic resistance worldwide, it is important that recommendations consider (in)appropriate antibiotics when there is an opportunity

to reduce resistance. This review found an important gap in antibiotics guidelines: resistance patterns were not considered by two third of recommendations for five highly prevalent infectious syndromes. Moreover, of the 251 recommendations, fewer than one in ten consistently reported data on their country specific resistance patterns. The recommendation would serve better the medical community if a specific antibiotic is preferred over the others, with the aim of providing appropriate coverage and minimizing spread and development of resistance. If resistance is not considered in guideline development, it is unlikely to be considered downstream. These data imply that significant changes are needed to the way resistance data is considered in recommendations for antibiotics.

Given the scarce attention to resistance, it is not surprising that evidence of substantial inappropriate or overuse of non-first-line antibiotics for most common conditions is prevalent in the medical literature. For instance data from the United States indicates that the problem of inappropriate antibiotic prescribing includes not only prescriptions that are unnecessary altogether, but also inappropriate selection of agents: physicians prescribed inappropriate antibiotics in about 30% to 50% of ambulatory adult consultations with suspected common infectious diseases[23,24]. However, when guidance is provided, evidence shows a more conscious use of antibiotics[25]. Since large areas of the world lack the infrastructure to collect resistance data, countries in need should be supported through international projects such as ReAct[26] or Ecumenical Pharmacy Network[27]. In the move towards better management of resistance, there is room for better standardization of approaches to include resistance on recommendations and better reporting of resistance data. Panels should scrutinize country-specific resistance data when considering antibiotic recommendations and should report the data, including important time trends. Guidelines certainly deserve attention, but implementation and quality improvement interventions are also important. Indeed, education and incentives that facilitate antibiotic optimal prescription should also be sustained by adequate policies. The quality of guidelines is closely intertwined with the quality of reporting. It is possible that guidelines took resistance patterns into consideration in their recommendations without mentioning it. Lack of details on how recommendations were developed leads users to assume that the quality was inadequate, unless information to the contrary is provided[28]. This is often justified because faulty reporting generally reflects faulty methods[29].

Although some findings are worrisome, other look more positive. One third of countries had at least one guideline on antibiotic use: even in the absence of published data, this number suggests that the guideline panels invested a remarkable amount of energy in this field. Fourteen countries produced more than 2 guidelines for at least one syndrome, raising concerns for duplication of efforts. The more prolific country, Spain, had a production of 13 documents, likely to generate redundancy and

confusion. Most guidelines were from high-income countries, with low- and lower-middle-income countries providing only 21%. Weak health care systems, including inadequate infrastructures for resistance collection, may justify the absence of epidemiologic and resistance data in these countries. Resistance patterns are highly heterogeneous: patterns in upper respiratory tract infections and UTIs are limited in comparison with CAPs. In the latter antibiotics and resistance may play a substantial role avoiding an evolution into life-threatening diseases. Paucity of resistance data in UTIs can be explained by the high probability of a viral etiology and a benign disease decourse. Antibiotics are not recommended as treatment by many scientific societies: the NICE guidelines (UK) did not include any antibiotic therapy in their guidance for these 3 syndromes[30]. This approach converges with the concept of wait and see prescription, to reduce unnecessary antibiotics use, which demonstrated to be efficient in the treatment of acute otitis media in children[31].

National and international recommendations should be accompanied by facility-specific antibiotic recommendations, particularly for common syndromes. Among the others, surgical prophylaxis has an important role as target of local stewardship programs. Most guidelines recommend a maximum postoperative duration of surgical antibiotic prophylaxis of 24 hours, but increasing evidence shows that using only a single preoperative dose (and possible additional intraoperative doses according to the duration of the operation) might be equally effective [32]. Prophylaxis use should be risk-adjusted according to surgical procedures to ensure that harms in terms of bacterial resistance do not outweigh the benefits. Implementation of a monitored antibiotic policies results in lower total antibiotic consumption, reduced antibiotic resistance, and reduced costs without increasing the risk of postoperative infections [33].

We recognize that our study can provide nothing more than a snapshot of the current state of the recommendations related to one dimension, antibiotic resistance. Comprehensive user-centered evaluations of the overall quality of guideline are needed. It was not our aim to assess whether recommendations have improved or worsened over time. Rather we sought to assess whether a problem existed at the time of our study. We did not investigate if recommendations on discrete resistance patterns were correct, or supported by evidence. The relevance of resistance patterns was not weighted. We accepted study authors' guidance on discrete patterns at face value, without further evaluating the quality of the recommendation. We adopted a non-validated arbitrary ordinal scale. Searches were done by a single researcher. We did not consider paper-based guidelines, which might be still prevalent in some contexts. Further research on the quality and relevance of specific recommendations based on resistance is needed identifying further obstacles to progress AMR and bringing them to light.

Conclusion

Our findings revealed that guidelines on empirical use of antibiotics do not provide meaningful information on resistance patterns and interpretation by decision makers is difficult because – as a principle – local resistance patterns should always be considered with empiric antibiotic choices. In appraising the evidence for antibiotic use guideline developers should be aware of the breadth and depth of overarching resistance issues. Awareness and understanding of AMR through surveillance and research are pillars of the WHO Global Action Plan on Antimicrobial Resistance. These results can be used by global initiatives such as the U.N. General Assembly High-Level Meeting on Antimicrobial Resistance and the Conscience of Antimicrobial Resistance Accountability (CARA) Alliance to monitor progress.

Figures

Figure 1. Flow chart of CPGs

Figure 2. Geographical distribution of CPGs (n=135)

List of Abbreviations

AB: Antibiotic

ABL: Apparented to β-lactam

AMN: Aminoglycoside

AMR: Antimicrobial Resistance

AOM: Acute Otitis Media

BLA: β-lactam

CAP: Community-Acquired Pneumonia

CAR: Carbapenem

CPG: Clinical Practice Guideline

EMRO: Eastern Mediterranean Regional Office

EURO: European Regional Office

FOF: Fosfomycin derivative

FQL: Fluoroquinolone

GLY: Glycopeptide

HIC: High-income Country

IMD: Imidazole derivative

IQR: Interquartile Range

LIC: Low-income Country

LMIC: Lower-middle Income Country

MDR: Multi Drug Resistant

MLS: Macrolide, Lincosamide, Streptogramin

MON: Monobactam

MRSA: Meticillin Resistant *Staphylococcus aureus*

NGO: Non-Governmental Organization

NICE: National Institute for Health and Care Excellence

NTF: Nitrofuran derivative

OXZ: Oxazolidinone

PAHO: Pan American Health Organization

PHA: Pharyngitis

PHE: Amphenicol

PRSP: Penicillin resistant *Streptococcus pneumoniae*

RHI: Rhinosinusitis

SEARO: South East Asia Regional Office

TET: Tetracycline

TMP: Trimethoprim derivative

UK: United Kingdom

UMIC: Upper-middle Income Country

UN: United Nations

URTI: Upper Respiratory Tract Infection

UTI: Urinary Tract Infection

WHO: World Health Organization

WPRO: West Pacific Regional Office

Ethics

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

CE, LM, DM, ML, GF and NM declare that they have no competing interests.

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Author's contribution

All authors made a substantial contribution to the conception and the design of the study. CE contributed to literature search and data collection. CE and LM contributed to the analysis. All authors participated in the interpretation of data. CE and LM drafted the initial manuscript. NM and GF coordinated the study. CE, LM, DM, ML, GF, and NM contributed to the review of the manuscript. All authors read and approved the final manuscript.

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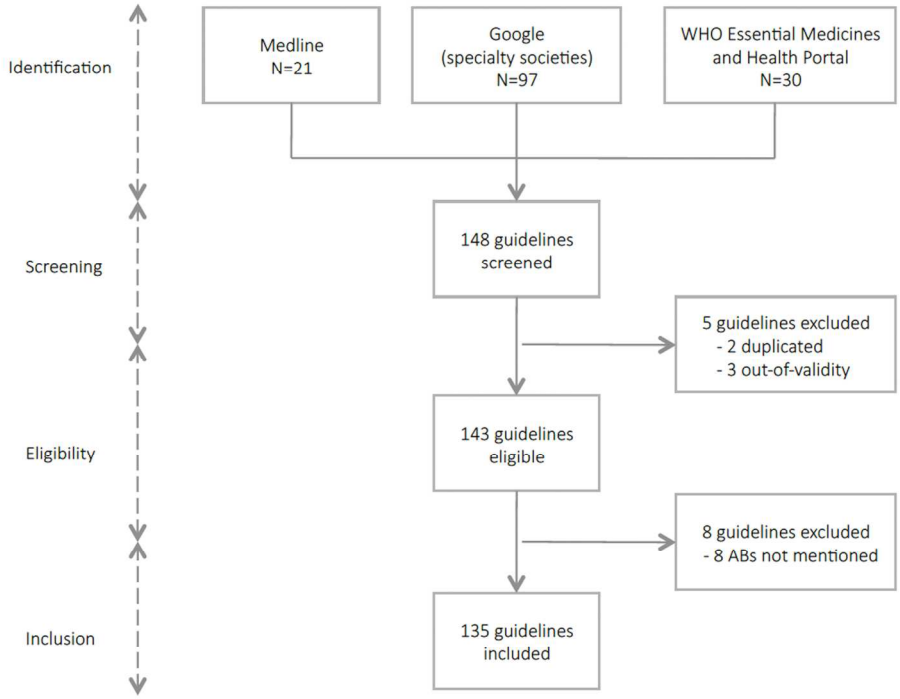

Figure 1. Flow chart of CPGs

173x132mm (300 x 300 DPI)

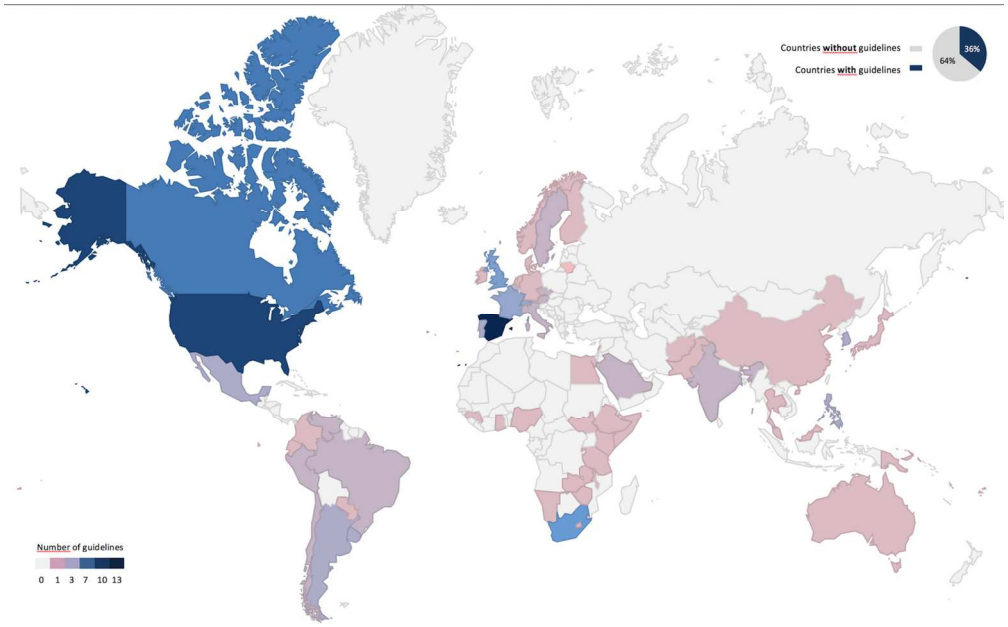

Figure 2. Geographical distribution of CPGs (n=135)

173x107mm (300 x 300 DPI)

ANNEXES

Supplementary Table 1. Antibiotic and resistance patterns in Community-Acquired Pneumonia (n=73)

	AMN	BLA	CAR	FQL	GLY	IMD	MLS	OXZ	PHE	TET	TMP
Recommendations considering resistance patterns											
Antibiotic used as an alternative because of high resistance rate	_	4(5.5%)	2(2.7%)	8(11.0%)	_	_	8 (11.0%)	_	_	5(6.8%)	1(1.4%)
Antibiotic not indicated because of high resistance rate	_	_	_	1(1.4%)	_	_	1 (1.4%)	_	_	1(1.4%)	_
Resistance risk	_	10(13.6%)	1(1.4%)	8(11.0%)	_	1 (1.4%)	5 (6.8%)	_	_	1(1.4%)	_
Resistance dosage	_	8(11.0%)	_	_	_	_	_	_	_	_	_
Atypical pathogens	_	_	_	2(2.7%)	_	_	17 (23.3%)	_	1(1.4%)	11(15%)	1(1.4%)
MRSA risk	_	_	_	_	5(6.8%)	_	3 (4.1%)	6(8.2%)	_	1(1.4%)	_
MDR risk	_	_	1(1.4%)	_	_	_	1 (1.4%)	_	_	_	_
PRSP risk	_	7(9.6%)	_	2(2.7%)	_	_	1 (1.4%)	_	_	_	_
Pseudomonas risk	9(12.3%)	14(19.1%)	12(16.4%)	10(13.7%)	_	_	9 (12.3%)	_	_	_	_
B-lactamase	1(1.4%)	7(9.6%)	_	1(1.4%)	_	1 (1.4%)	1 (1.4%)	_	_	_	_

AMN: Aminoglycosides; **BLA:** βlactam; **CAR**: Carbapenems; **FQL** : Fluoroquinolone ; **GLY** : Glycopeptids ; **IMD** : Imidazoles derivates ; **MLS** : Macrolides, Lincosamides, Streptogramins **; OXZ :** Oxazolidinones ; **PHE** : Amphenicoles : **TET** : Tetracyclines ; **TMP** : Trimetoprim derivates; **Resistance risk** : antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months) ; **Resistance dosage** : antibiotic used at high dosage if there is a risk of resistant strains ; **Atypical pathogens** : Risk of atypical pathogens ; **MRSA risk :** Risk of meticillin-resistant *Staphylococcus aureus* (MRSA) ; **MDR risk** : Risk of Multi Drug Resistant strains ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumonia* (PRSP) ; **Pseudomonas risk** : Risk of *Pseudomonas aeruginosa* ; **βlactamase risk** :Risk of strains producing β-lactamase

Supplementary Table 2. Antibiotic and resistance patterns in Urinary Tract Infections (n=63)

	ABL	AMN	BLA	CAR	FOF	FQL	NTF	TMP
Recommendations considering resistance patterns								
Antibiotic used as an alternative because of high resistance rate	_	_	5 (7.9%)	_	1 (1.6%)	8(12.7%)	_	2(3.2%)
Antibiotic not indicated because of high resistance rate	_	_	5(7.9%)	_	_	2(3.2%)	_	1(1.6%)
Resistance risk	_	3 (4.8%)	1 (1.6%)	1 (1.6%)	_	2(3.2%)	2(3.2%)	1(1.6%)
Resistance AB	_	2 (3.2%)	2(3.2%)	_	1(1.6%)	1(1.6%)	_	1(1.6%)
Resistance threshold	1(1.6%	_	_	_	_	2(3.2%)	_	8 (12.7%)
MDR risk	_	2(3.2%)	_	2(3.2%)	_	_	_	_

ABL: Apparented to βlactam **; AMN**: Aminoglycosides ; **BLA :** βlactam ; **CAR** : Carbapenems; FOF : Fosfomycin derivates ; **FQL** : Fluoroquinolone ; **NTF:** Nitrofuran ; **TMP** : Trimetoprim derivates **; Resistance risk** : antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months) ; **Resistance threshold** : antibiotic used only under a certain threshold of resistance ; **Resistance AB** : antibiotic used if first line AB is resistant ; **MDR risk** : Risk of Multi Drug Resistant strains

Supplementary Table 3. Antibiotic and resistance patterns in Acute Otitis Media (n=42)

	BLA	FQL	MLS	OXZ	TMP
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	4 (9.5%)	_	3 (7.1%)	_	_
Antibiotic not indicated because of high resistance rate	_	_	_	_	1 (2.4%)
Resistance risk	4 (9.5%)	_	_	_	_
Resistance dosage	7 (16.7%)	_	_	_	_
MDR risk	_	1 (2.4%)	_	1 (2.4%)	_
PRSP risk	5 (11.9%)	_	1 (2.4%)	_	_
B-lactamase	11 (26.2%)	_	_	_	_

BLA : βlactam ; **FQL** : Fluoroquinolone ; **MLS** : Macrolides, Lincosamides, Streptogramins ; **OXZ :** Oxazolidinones ; **TMP** : Trimetoprim derivates ; **Resistance risk** : antibiotic used only if there is a risk of increasing resistance (e.g. recent use of critical AB during past months); **Resistance dosage** : antibiotic used at high dosage if there is a risk of resistant strains ; **MDR risk** : Risk of Multi Drug Resistant strains ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumonia* (PRSP) ; **β-lactamase risk** :Risk of strains producing βlactamase

Supplementary Table 4. Antibiotic and resistance patterns in Rhinosinusitis (n=39)

	BLA	FQL	MLS	OXZ	TMP
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	1 (2.6%)	3 (7.7%)	_	_	_
Antibiotic not indicated because of high resistance rate	2 (5.1%)	_	3 (7.7%)	_	3 (7.7%)
Resistance risk	2 (5.1%)	2 (5.1%)	_	_	_
Resistance dosage	8(20.5%)	_	_	_	_
Resistance threshold	_	_	2 (5.1%)	_	_
PRSP risk	5(12.8%)	_	1 (2.6%)	1 (2.6%)	_
B-lactamase	8(20.5%)	_	_	_	_

BLA : βlactam ; **FQL** : Fluoroquinolone ; **MLS** : Macrolides, Lincosamides, Streptogramins ; **OXZ :** Oxazolidinones ; **TMP** : Trimetoprim derivates **; Resistance risk** : antibiotic used only if there is a risk of increasing resistance (recent use of critical AB during past months) ; **Resistance dosage** : antibiotic used at high dosage if there is a risk of resistant strains ; **Resistance threshold** : antibiotic used only under a certain threshold of resistance ; **PRSP risk** : Risk of penicillin resistant *Streptococcus pneumonia* (PRSP) ; **β-lactamase risk** :Risk of strains producing β-lactamase

Supplementary Table 5. Antibiotic and resistance patterns in Pharyngitis (n=34)

	BLA	FQL	MLS	TET	TMP
Recommendations considering resistance patterns					
Antibiotic used as an alternative because of high resistance rate	1 (2.9%)	_	_	_	_
Antibiotic not indicated because of high resistance rate	2 (5.9%)	1 (2.9%)	_	2 (5.9%)	1 (2.9%)
Resistance threshold	_	_	2 (5.9%)	_	_
Atypical pathogens	_	_	1 (2.9%)	_	_

BLA : βlactam ; **FQL** : Fluoroquinolone ; **MLS** : Macrolides, Lincosamides, Streptogramins ; **TET** : Tetracyclins ; **TMP** : Trimetoprim derivates ; **Resistance threshold** : antibiotic used only under a certain threshold of resistance ; **Atypical pathogens** : Risk of atypical pathogens